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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/728,323	CAPLAN, MICHAEL J.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/21/08; 2/29/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-49* is/are pending in the application.

4a) Of the above claim(s) *37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-36 and 38-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 34-49 are pending.

2. Claim 37 stands withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

3. Claims 34-36 and 38-49, drawn to a composition comprising dead *E. coli* containing therein at least one modified peanut allergen whose amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or crosslink IgE as compared with the wild-type peanut allergen are being acted in this Office Action.

4. In view of the amendment filed October 21, 2008, the following rejections remain.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 34-36, 38-45 and 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/38978 publication (of record, Aug 1999, PTO 1449) in view of Fenton et al (of record, J National Cancer Institute 87(24): 1853-1861, December 1995; PTO 892), Vrtala et al (of record, Int Arch Allergy Immunol 107: 290-294, 1995; PTO 1449), US Pat No 5,888,799 (newly cited, issued March 30, 1999; PTO 892), US Pat No. 3,097,141 (newly cited, issued July 9, 1963; PTO 892) and Leclerc et al (of record, J Immunology 144(8): 3174-3182, 1990; PTO 892).

The WO 99/38978 publication teaches a composition comprising *E coli* comprising at least one recombinant modified allergen such as modified peanut allergen Ara h1, Ara h2 and Ara h3 where the center of one or more amino acid present in IgE binding sites of Ara h1, Ara h2 and Ara h3 have been substituted with neutral or hydrophilic amino acid or lacks a portion of the wild-type peanut allergen such that the modified peanut allergens have reduced binding to IgE as

compared to the wild-type (see page 3, line 22-30, page 10, line 10-16, page 16, line 22-33, claims 1-7 of the WO 99/38978 publication, in particular). The reference wild-type Ara h3 allergen of SEQ ID NO: 6 is encoded by the reference nucleotide sequence of SEQ ID NO: 5, which is identical to the claimed SEQ ID NO: 3 (see reference SEQ ID NO: 5, in particular). The reference IgE binding sites of Ara h1, Ara h2 and Ara h3 are shown in Table 4 at page 23, Table 5 at page 24 and Table 6 at page 24, respectively. The reference wild-type Ara h1 of SEQ ID NO: 2 is encoded by the reference SEQ ID NO: 1. The reference wild-type Ara h2 of SEQ ID NO: 4 is encoded by the reference SEQ ID NO: 3. The reference further teaches a method of making modified allergen such as peanut protein Ara h1, Ara h2, Ara h3 or a portion thereof wherein the modified peanut allergen or portion thereof has at least one amino acid that has been deleted or substituted within the IgE binding sites such that the modified protein has a reduced ability to bind and crosslink IgE antibodies (See Abstract, page 19, reference SEQ ID NO: 2, 4 and 6, claims 14, 17-20, 23 and 36 of WO 99/38978 publication, claims 29-in particular). The reference modified peanut allergen is encapsulated inside the dead *E coli* because the recombinant modified protein is expressed as inclusion bodies which located in the cytoplasm since it must be solubilized with urea (See claim 27 of WO 99/38978 publication, page 16, lines 30-32, in particular). The WO 99/38978 publication further teaches the critical amino acids within each of the IgE binding epitope of the peanut protein such as Ara h1, Ara h2 and Ara h3 that are important for IgE binding and substitution of a specific single amino acid within each of the identified epitope abolishes IgE binding (See abstract, page 18, Table 4, Table 5 and Table 6, in particular). The reference's modified peanut allergens Ara h1, Ara h2 and Ara h3 are identical to the ones to be incorporated by reference to 09/141,220. The WO 99/38978 publication teaches the modified peanut allergen is safe and efficacious for treating peanut allergy (see page 2, lines 21, claim 36 of the publication, in particular). The advantage of having IgE binding sites converted to non-IgE binding sites by masking the site or by single amino acid substitution within the center of IgE binding would be useful for immunotherapy (see abstract, page 10, in particular).

The claimed invention differs from the teachings of the reference only in that the composition comprising modified allergen encapsulated in *E coli* wherein the *E coli* is dead instead of alive and the *E coli* was killed by heat.

Fenton et al teach a pharmaceutical composition comprising dead *Escherichia coli* that have been engineered to express recombinant modified ras protein bearing a Gln to Leu mutation

at residue 61 and a pharmaceutical carrier such as Hanks Balance Salt solution or HBSS (see page 1855, col. 1, Immunization with heat-killed bacteria, in particular). The reference *E coli* were heat-killed by incubation at 56°C for 40 minutes (see page 1855, col. 1, second paragraph, in particular). The reference recombinant Ras protein obviously located in side the *E coli* such as inclusion bodies located within the cytoplasm given the purification of Ras protein must be disrupted with sonification (see page 1854, col. 2, Purification of Ras proteins, in particular). Fenton et al further teach antigen presenting cell such as macrophage can phagocytose genetically engineered *E coli* and present the recombinant modified protein derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity by modulating immune response to Th1 as measured by cytokines IL-2, IFNγ secreted and granuloma formation at the vaccine site (see page 1857, col. 2, full paragraph, page 1860, col. 2, second full paragraph, in particular).

Vrtala et al teach the use of recombinant non-pathogenic *Salmonella* genetically engineered to express modified birch pollen allergen Bet vI localized to the cytoplasm of *Salmonella* and mice fed with Salmonella expressing Bet vI can develop a Bet vI allergen specific Th1 immune response (see page 293, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification (see page 293, col. 2, in particular). However, there are a number of technical and ethical problems before such *live* allergy vaccines could be used for therapy of type I allergy in patients (see page 293, col. 2, in particular).

The ‘799 patent teaches the use of *E coli* bacteria as an antigen or allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). The reference *E coli* can be viable or non-viable upon the death of the micro, the antigen will be made available by the carrier and releases cytoplasmic and/or periplasmic antigens (see col. 9, lines 3-40, in particular). The ‘799 patent teaches the antigen or allergen of interest in the *E coli* can be engineered to transport across the E coli cytoplasmic membrane end ended up in the periplasmic space (see col. 14, line 29-31, in particular). The bacterial cell is formulated for administered orally in enteric-coated capsules (see col. 13, line 4-6, in particular).

The ‘141 patent teaches a method of modifying anaphylactogens which reduces toxicity and preventing hypersensitivity while retaining antigenicity of *E coli* by heating *E coli* from about

50 to 100 °C to reduce toxicity of the antigens (see col. 1, lines 8-65, col. 2, line 1-10, in particular). The '141 patent further teaches *E coli* can be killed by chemical treatment such as phenol (see col. 1, line 31, in particular) or oxidizing agent such as hydrogen peroxide H_2O_2 (see col. 1, line 58, in particular).

Leclerc et al teach a pharmaceutical composition comprising heat-killed recombinant *E coli* expressing any antigen of interest such as foreign poliovirus epitopes or hepatitis B virus antigen in the periplasm instead of cytoplasm and a pharmaceutical acceptable carrier such as PBS (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). Leclerc et al teach good antibody responses were development after injection of heat-killed bacteria by the s.c. or i.v. route (see page 3177, col. 1, Figure 3, Table II, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the *E coli* bacteria that expressed the modified peanut allergen Ara h1, Ara h2 and Ara h3 with reduced ability to bind to or cross-link IgE of the WO 99/38978 publication as an allergen carrier for induction of tolerance as taught by the '799 patent by killing the bacteria with heat such as heating from about 50 to 100 °C as taught by Fenton or the '141 patent or Lecberc et al or kill by oxidizing agent such as hydrogen peroxide as taught by the '141 patent to avoid any technical and ethical issues without the need for extensive protein purification using such bacteria for treating allergy as taught by Vrtala et al.

One having ordinary skill in the art at the time the invention was made would have been motivated to modify peanut allergen because peanut is highly anaphylactic and the advantage of having IgE binding sites converted to non-IgE binding sites by *masking* the IgE site or by single amino acid substitution within the center of IgE binding site of the peanut protein such as Ara h1, Ara h2 and Ara h3 would be useful for immunotherapy as taught by the WO 99/38978 publication (see abstract, page 10, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use killed bacteria *E coli* expressing modified food allergen because Vrtala et al teach killing the microorganism that expressed modified allergen can avoid the ethical problems associated with using *live* microorganism for allergy vaccines or therapy of type I allergy in patients (see page 293, col. 2, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification (see page 293, col. 2, in particular). One having ordinary skill in the art at the time

the invention was made would have been motivated with the expectation of success to use killed bacteria as vaccine carrier because Fenton et al teach heat-killed recombinant *E coli* is useful as a vaccine since antigen presenting cell such as macrophage can phagocytose the bacteria *E coli* and present the peptides derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity, and to modulate immune response to Th1 as measured by cytokines IL-2, IFNγ secreted (see page 1857, col. 2, full paragraph, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use heat-killed *E coli* bacteria because Leclerc et al teach good antibody responses were development after injection of heat-killed *E coli* bacteria expressing the antigen of interest by the s.c. or i.v. route (see page 3177, col. 1, Figure 3, Table II, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use bacteria E coli as a vaccine carrier because the '799 patent teaches microorganism such as *E coli* can be use as an antigen or allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to kill bacteria with heat because the '141 patent teaches heat killing *E coli* can reduce toxicity and preventing hypersensitivity while retaining antigenicity of *E coli* (see col. 1, lines 8-65, col. 2, line 1-10, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention. Claim 43 is included in this rejection because it is obvious that IgE binding to modified peanut allergen cannot be detected without disrupting the dead *E coli* with urea since the modified allergen can be engineered to located as inclusion bodies located within the cytoplasm as taught by Fenton et al, or can be engineered to transport across the *E coli* cytoplasmic membrane end ended up in the periplasmic space instead of cytoplasm as taught by the '799 patent or Leclerc et al. Claim 44 is included in this rejection because a composition is a composition, irrespective of its intended use such as adapted for rectal administration. The heat-killed *E coli* in the pharmaceutical composition as taught by Fenton et al could be adapted for rectal administration.

Applicants' arguments filed October 21, 2008 and February 29, 2008 have been fully considered but are not found persuasive.

Applicants' position is that the '978 publication, whether alone or in combination with any of the cited references, does not teach or suggest a modified allergen "encapsulated inside"

dead *E. coli,* as recited in the present claims. Furthermore, the '978 publication does not teach or suggest *any pharmaceutical composition* comprising encapsulated modified allergens, as recited in the present claims. Indeed, as has been extensively discussed, several of the secondary references *teach explicitly away* from the claimed invention. To give but one example, some secondary references *require live* bacteria. There is absolutely no combination of these cited references that could teach or suggest the claimed invention.

The *sole* statement made by the Examiner with regard to "encapsulated inside" is that urea is used to solubilize a protein produced in the '978 publication. This statement is wholly irrelevant to the present claims.

First, the protein being solubilized with urea in the '978 publication is *not* a modified peanut allergen as recited in the present claims. That is, the '978 publication is describing urea purification of a *different protein.*

Second, the fact that the '978 inventors used urea in purifying a protein does not mean that the protein is "encapsulated within" bacteria.

Third, clearly, if the '978 inventors are isolating *protein from* dead *E. coli,* they are not preparing the dead *E. coli* as a *pharmaceutical composition,* as recited in the present claims.

For all of these reasons, the '978 publication cannot teach or suggest *pharmaceutical compositions* of *modified* allergens *encapsulated inside* dead *E. coli.* The Examiner cannot continue to ignore these points.

No list of secondary references, however long, is meaningful unless the cited secondary references in fact address the deficiencies of the primary reference. Moreover, the Examiner must take the teachings of the secondary references *as a whole* and may not ignore those portions that inconveniently teach away from the Examiner's intended combination, or from the claimed invention.

The "new" rejections levied in the Office Action add nothing substantive to the previously-levied rejections, yet the Office Action has not a single remark addressing, or even acknowledging, Applicant's prior arguments or amendments made in the Response submitted on February 29, 2008.

In response to the argument that the ‘978 publication does not teach or suggested a modified allergen "encapsulated inside" dead *E coli*, as recited in the present claims, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Contrary to applicants' assertion that the WO/38978 publication does not teach modified allergen, the WO/38978 publication teaches production of recombinant modified allergen such as modified peanut allergen Ara h1 (Table 4), modified peanut allergen Ara h2 (Table 2) and modified peanut allergen (Table 6), see reference page 10, lines 10-16, Table 4-6, in particular. The recombinant modified allergen is expressed in host cell such as bacteria *E coli* strain BL21 (DE3), see page 10, line 13, page 16, line 29, in particular. In fact, the instant specification at page 44 discloses the use of the same bacteria *E coli* strain BL21 (DE3) as disclosed by the WO/38978 publication. Further, page 27 of instant specification discloses production of recombinant or modified allergen, See page 27, lines 4-8. The reference recombinant modified allergen in the *E coli* is not secreted (encapsulated inside the E coli) because the recombinant modified protein is expressed as inclusion bodies which located in the cytoplasm and must be lysis in denaturing binding buffer such as urea (See claim 27 of WO 99/38978 publication, page 16, lines 30-32, in particular).

The claimed invention differs from the teachings of the reference only in that the composition comprising modified allergen encapsulated in *E coli* wherein the *E coli* is dead instead of alive and the *E coli* was killed by heat.

However, Fenton et al teach the use of dead *E coli* expressing recombinant antigen of interest as a carrier for a pharmaceutical composition.

Likewise, the '799 patent teaches also the use of dead *E coli* bacteria as an allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). The reference *E coli* can be viable or non-viable since upon the death of the micro, the antigen or allergen will be made available by the carrier and releases cytoplasmic and/or periplasmic antigens (see col. 9, lines 3-40, in particular).

Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen as a carrier for treating allergy without having the need for extensive protein purification (see page 293, col. 2, in particular).

The '141 patent teaches a method of modifying anaphylactogens which reduces toxicity and preventing hypersensitivity while retaining antigenicity of *E coli* by heating *E coli* from about 50 to 100 °C to reduce toxicity of the antigens (see col. 1, lines 8-65, col. 2, line 1-10, in

particular). The '141 patent further teaches *E coli* can be killed by chemical treatment such as phenol (see col. 1, line 31, in particular) or oxidizing agent such as hydrogen peroxide H_2O_2 (see col. 1, line 58, in particular).

Leclerc et al teach a pharmaceutical composition comprising heat-killed recombinant *E coli* expressing any antigen of interest such as foreign poliovirus epitopes or hepatitis B virus antigen in the periplasm instead of cytoplasm and a pharmaceutical acceptable carrier such as PBS (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the *E coli* bacteria that expressed the modified peanut allergen Ara h1, Ara h2 and Ara h3 with reduced ability to bind to or cross-link IgE of the WO 99/38978 publication as an allergen carrier for induction of tolerance as taught by the '799 patent by killing the bacteria with heat such as heating from about 50 to 100 °C as taught by Fenton or the '141 patent or Lecberc et al or kill by oxidizing agent such as hydrogen peroxide as taught by the '141 patent to avoid any technical and ethical issues without the need for extensive protein purification using such bacteria for treating allergy as taught by Vrtala et al.

One having ordinary skill in the art at the time the invention was made would have been motivated to modify peanut allergen because peanut is highly anaphylactic and the advantage of having IgE binding sites converted to non-IgE binding sites by *masking* the IgE site or by single amino acid substitution within the center of IgE binding site of the peanut protein such as Ara h1, Ara h2 and Ara h3 would be useful for immunotherapy as taught by the WO 99/38978 publication (see abstract, page 10, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use killed bacteria *E coli* expressing modified food allergen because Vrtala et al teach killing the microorganism that expressed modified allergen can avoid the ethical problems associated with using *live* microorganism for allergy vaccines or therapy of type I allergy in patients (see page 293, col. 2, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification (see page 293, col. 2, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use killed bacteria as vaccine carrier because Fenton et al teach heat-killed recombinant *E coli* is useful as a vaccine since antigen presenting cell such as macrophage can phagocytose the bacteria *E coli* and

present the peptides derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity, and to modulate immune response to Th1 as measured by cytokines IL-2, IFNγ secreted (see page 1857, col. 2, full paragraph, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use heat-killed *E coli* bacteria because Leclerc et al teach good antibody responses were development after injection of heat-killed *E coli* bacteria expressing the antigen of interest by the s.c. or i.v. route (see page 3177, col. 1, Figure 3, Table II, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use bacteria E coli as a vaccine carrier because the '799 patent teaches microorganism such as *E coli* can be use as an antigen or allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to kill bacteria with heat because the '141 patent teaches heat killing *E coli* can reduce toxicity and preventing hypersensitivity while retaining antigenicity of *E coli* (see col. 1, lines 8-65, col. 2, line 1-10, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

With respect to the argument that the '978 publication does not teach or suggest any pharmaceutical composition, it is noted that none of the rejected claims recite "pharmaceutical composition". Furthermore, Leclerc et al teach a pharmaceutical composition comprising heat-killed recombinant *E coli* expressing any antigen of interest wherein the antigen is encapsulated in the periplasm instead of secreted and a pharmaceutical acceptable carrier such as PBS (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). The '799 patent teaches pharmaceutical composition comprising *E coli* bacteria expressing antigen or allergen as a carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). The reference *E coli* can be viable or non-viable since upon the death of the micro, the antigen/allergen will be made available by the carrier and releases cytoplasmic and/or periplasmic antigens (see col. 9, lines 3-40, in particular).

With respect to the argument that secondary reference teach explicitly away from the claimed invention such as require *live* bacteria instead of dead bacteria, Leclerc et al teach a pharmaceutical composition comprising heat-killed or dead recombinant *E coli* expressing any antigen of interest wherein the antigen is encapsulated in the periplasm instead of secreted and a

pharmaceutical acceptable carrier such as PBS (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). Further, the recitation of "dead" *E coli* is an obvious variation of the teachings of the reference '799 patent since the '799 patent teaches *E coli* can be viable or non-viable upon the death of the micro, the antigen will be made available by the bacteria carrier and releases cytoplasmic and/or periplasmic antigens (see col. 9, lines 3-40, in particular).

With respect to the argument that the '978 publication used urea in purifying a protein does not mean that the protein is "encapsulated within" bacteria, at the very least, the protein is not secreted. Since the protein is not secreted, then the protein must be encapsulated. Even assuming the '978 publication does not teach encapsulated protein as argued, Leclerc et al teach a pharmaceutical composition comprising heat-killed recombinant *E coli* expressing any antigen of interest in the periplasm (which meets the definition of encapsulated within the bacteria) instead of cytoplasm and a pharmaceutical acceptable carrier such as PBS (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). The '799 patent teaches allergen encapsulated in the *E coli* such as cytoplasmic and/or periplasmic allergen released by the carrier upon death of the bacteria (see col. 9, lines 3-40, in particular). Finally, it is noted that the specification discloses the dead E coli expressing the modified peanut allergens is encapsulated in PLGA, chitosan, lipsomes or hydrogel, see page 34.

With respect to the argument that the '978 publication describes expression of a wild type allergen (i.e., Ara h2) and not modified allergen, the '978 publication exemplified recombinant expression of wild type allergen i.e., Ara h2, see page 16. In addition, the WO/38978 publication teach recombinant production of modified allergen, see page 10. The WO/38978 publication teaches production of recombinant modified allergen such as modified peanut allergen Ara h1 (Table 4), modified peanut allergen Ara h2 (Table 2) and modified peanut allergen (Table 6), see reference page 10, lines 10-16, Table 4-6, in particular. The recombinant production is expressed in host cell including bacteria, see page 10, lines 10-13, in particular.

With respect to the argument that the Fenton et al teach a pharmaceutical composition comprising dead *E. coli* that express a particular modified Ras protein and not modified allergen that will be used to immunize a subject and teaches away from immunization using cells comprising modified allergens, Fenton teach the use of dead *E coli* expressing an antigen of interest as a carrier for a pharmaceutical composition. Likewise, the '799 patent teaches the use

of dead *E coli* bacteria as an allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). Although Fenton et al and the '799 patent do not teach the modified peanut allergen, the '978 publication teaches modified peanut allergens and expressed in *E coli* discussed supra.

A prior art reference from a different field may serve as analogous art if it is reasonably pertinent to the problem addressed by the application, see *In re Icon Health & Fitness*, Inc. No. 06-1573 (Fed. Cir. Aug. 1, 2007). In this case, the use as dead *E coli* as antigen carrier for vaccine or pharmaceutical composition is well known in the field of vaccine immunology at the time of the invention may have led one skilled in the art to look into Leclerc et al who teach encapsulated heat-killed recombinant *E coli* expressing any antigen of interest such as foreign poliovirus epitopes or hepatitis B virus antigen in the periplasm instead of cytoplasm as a vaccine carrier (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). Likewise, Fenton et al teach the use of dead *E coli* expressing recombinant antigen of interest as a carrier for a pharmaceutical composition. The '799 patent also teaches the use of live or dead *E coli* bacteria as an allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). The reference *E coli* can be viable or non-viable upon the death of the micro, the antigen will be made available by the carrier and releases cytoplasmic and/or periplasmic antigens (see col. 9, lines 3-40, in particular). The *E coli* as carrier can be killed by heat or chemical as taught by the '141 patent. The expected advantage of using bacteria expressing modified allergen as allergy vaccine is that it does not have the need for extensive protein purification using bacteria transformed with any cDNA encoding the modified allergen of interest as taught by Vrtala et (see page 293, col. 2, in particular).

Contrary to applicants' assertion that there is no motivation for one of ordinary skill to modify the teachings of the '978 publication to achieve encapsulation of (1) modified allergen; in (2) dead *E coli* that were (3) killed by heat, the strongest rationale for combining references is a recognition in the art that some advantage or expected beneficial result would have been produced by their combination. This recognition may be an expressed statement in a reference, an implication that can be drawn from one or more references or a convincing line or reasoning based upon established principles or legal precedent.

In this case, one having ordinary skill in the art at the time the invention was made would have been motivated to modify peanut allergen because peanut is highly anaphylactic and the advantage of having IgE binding sites converted to non-IgE binding sites by *masking* the IgE site or by single amino acid substitution within the center of IgE binding site of the peanut protein such as Ara h1, Ara h2 and Ara h3 would be useful for immunotherapy as taught by the WO 99/38978 publication (see abstract, page 10, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use killed bacteria *E coli* expressing modified food allergen because Vrtala et al teach killing the microorganism that expressed modified allergen can avoid the ethical problems associated with using *live* microorganism for allergy vaccines or therapy of type I allergy in patients (see page 293, col. 2, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification (see page 293, col. 2, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use killed *E coli* bacteria as vaccine carrier because Fenton et al teach heat-killed recombinant *E coli* is useful as a vaccine since antigen presenting cell such as macrophage can phagocytose the bacteria *E coli* and present the peptides derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity, and to modulate immune response to Th1 as measured by cytokines IL-2, IFNγ secreted (see page 1857, col. 2, full paragraph, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use heat-killed *E coli* bacteria because Leclerc et al teach good antibody responses were development after injection of heat-killed *E coli* bacteria expressing the antigen of interest by the s.c. or i.v. route (see page 3177, col. 1, Figure 3, Table II, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use bacteria *E coli* as a vaccine carrier because the '799 patent teaches microorganism such as *E coli* can be use as an antigen or allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to kill bacteria with heat because the '141 patent teaches heat killing *E coli* can reduce toxicity and preventing hypersensitivity while retaining antigenicity of *E coli* (see col. 1, lines 8-65, col. 2, line 1-10, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007)* and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according known methods to yield predictable results.

B) Simple substitution of one known element for another to obtain predictable results.

C) Use of known technique to improve similar products in the same way.

D) Applying known technique to a known product ready for improvement to yield predictable results.

E) "Obvious to try" --- choosing form a finite number of identified, predictable solutions, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

Since recombinant production of modified peanut allergen in *E coli* is known at the time of the invention and combining the prior art elements of using dead *E coli* (killed by heat or chemical) expressing modified allergen in periplasm (encapsulated) or cytoplasm as a carrier for induction of tolerance is desirable and have been predictable at the time the invention was made, there would have been reasonable expectation of success in combine the references teachings to arrive at the claimed invention. An obviousness is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007).* From the combined teachings

of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

With respect to the argument that Vrtala et al teach feeding of recombinant attenuated Salmonella that express modified birch pollen allergens to mice and does not teach dead *E coli*, as stated above, Leclerc et al teach a pharmaceutical composition comprising heat-killed recombinant *E coli* expressing any antigen of interest. Likewise, the '799 patent teaches also the use of dead *E coli* bacteria as an allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). Vrtala et al is merely cited for the advantage of using bacteria transformed with any cDNA coding for the modified allergen as a vaccine carrier without having the need for extensive protein purification (see page 293, col. 2, in particular). As applicants pointed out, Vrtala et al teach the ethical problems associated live allergy vaccine, Vrtala et al offers one solution of using attenuated bacteria to express modified allergen. Although Vrtala et al does not teach dead *E coli*, Leclerc et al teach heat-killed recombinant *E coli* expressing any antigen of interest. The '799 patent teaches also the use of dead *E coli* bacteria as an allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular).

Contrary to applicants' assertion that the secondary references teach away the claimed invention, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed.." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

7. Claims 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/38978 publication (of record, Aug 1999, PTO 1449) in view of Fenton et al (of record, J National Cancer Institute 87(24): 1853-1861, December 1995; PTO 892), Vrtala et al (of record, Int Arch Allergy Immunol 107: 290-294, 1995; PTO 1449), US Pat No 5,888,799 (newly cited, issued March 30, 1999; PTO 892), US Pat No. 3,097,141 (newly cited, issued July 9, 1963; PTO 892) and Leclerc et al (of record, J Immunology 144(8): 3174-3182, 1990; PTO 892) as applied to claims 34-36, 38-45 and 48-49 mentioned above and further in view of WO 92/14487 (newly cited published September 1992; PTO 892), US Pat No 6,270,723 (of record, filed Oct 2, 1998;

PTO 892), Komanapalli et al (newly cited, Appl Microbil Biotechnol 49: 766-769, 1998; PTO 892) and/or Ingram et al (newly cited, J Bacteriology 144(2): 481-488, Nov 1980; PTO 892).

The combined teachings of the WO 99/38978 publication, Fenton et al, Vrtala et al, the '799 patent, the '141 patent and/or Leclerc et al have been discussed supra.

The claimed invention in claim 46 differs from the combined teachings of the references only in that composition wherein the *E coli* was killed using a chemical instead of heat.

The claimed invention in claim 47 differs from the combined teachings of the references only in that composition wherein the *E coli* was killed using a chemical selected from the group consisting of iodine, bleach, ozone, and alcohols instead of heat.

The WO 92/14487 publication teaches a method of safely killing *E coli* bacteria expressing various colonization factor antigens by chemical treatment such as mild or diluted formalin-treated *E coli* for use as a whole cell vaccine (see page7-8, page 19, line 26, in particular). The WO 92/14487 publication teaches the advantage of formalin-killed bacteria is that it would safely kill the *E coli* bacteria and at the same time preserving the antigenic properties of the antigen expressed in *E coli* as well as greater stability of the antigen against degradation in the intestinal milieu (see page 8, lines 7-9, in particular).

The '723 patent teaches various methods of killing *bacteria* by chemical treatment such as alcohol (see col. 1, line 21, in particular), bleach (see col. 10, line 39-40, in particular) or pressure sterilization (ozone) to inactivate bacteria such as *E coli* for pharmaceutical composition (see col. 11, lines 42-67, col. 15, line 8, in particular). The '723 patent teaches these methods can improve the safety of vaccine or any product used by patient (see col. 8, lines 26-67, col. 9, lines 1-15, in particular).

Komanapalli et al teach ozone treatment resulted in a time-dependent decrease of cell viability of *E coli* while oxygen gas has no effect (see page 767, col. 2, results, Fig. 1, in particular). Ozone induced lipid oxidation in *E coli* and leakage of cytoplasmic contents (see abstract, see Figs 5 & 6, in particular).

Ingram et al teach alcohols and other amphipathic molecules have long been used as antimicrobial agents to prevent the growth of bacteria (see page 484, col. 2, Discussion, in particular). Ingram et al teach increasing concentrations of alcohol such as ethanol and hexanol progressively inhibits the growth of E coli and hexanol was a much more potent inhibitor of growth than was ethanol (see page 482, col. 2, in particular). Ingram et al teach ethanol

prevented the assembly of cross-linked peptidoglycan while hexanol did not inhibit such cross-linking, see page 485, col. 2, in particular.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made with the expectation of success to kill any recombinant modified peanut allergen producing *E. coli* bacteria for a pharmaceutical composition given the highly anaphylactic nature of the peanut allergen as taught by the WO 99/38978 publication by means chemical treatment such as mild or diluted formalin-treatment as taught by the WO 92/14487 publication or diluted alcohol (see col. 1, line 21, in particular), or diluted bleach (see col. 10, line 39-40, in particular) as taught by the '723 patent instead of heat as taught by Fenton et al or by different types of alcohol as taught by Ingram or by ozone as taught by Komanapalli et al to preserve the immunogenic property of inactivated bacteria as taught by the WO 92/14487 publication.

One having ordinary skill in the art would have been motivated to kill *E coli* bacteria expressing modified peanut allergen because peanut allergens are highly anaphylactic as taught by the WO 99/38978 publication. One having ordinary skill in the art would have been motivated to kill *E coli* bacteria expressing modified peanut allergen with any conventional chemical because the advantage of formalin-killed bacteria is that it would safely kill the *E coli* bacteria and at the same time preserving the antigenic properties of the antigen expressed in *E coli* as well as maintaining greater stability of the antigen against degradation in the intestinal milieu as taught by the WO 92/14487 publication (see page 8, lines 7-9, in particular). The '723 patent teaches chemical treatment such as iodine, bleach, ozone, or alcohol can improve the safety of vaccine or any product used by patient (see col. 8, lines 26-67, col. 9, lines 1-15, in particular). Ingram et al teach alcohols and other amphipathic molecules have long been used as antimicrobial agents to prevent the growth of bacteria (see page 484, col. 2, Discussion, in particular). Komanapalli et al teach ozone treatment resulted in a time-dependent decrease of cell viability of *E coli* (see page 767, col. 2, results, Fig. 1, in particular). The motivation to kill the modified peanut allergen expressed in *E coli* for a pharmaceutical composition is obvious given the ethical problems for using live bacteria as allergy vaccines in patients as taught by Vrtala et al (see page 293, col. 2, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Applicants' arguments filed October 21, 2008 and February 29, 2008 have been fully considered but are not found persuasive for the same reasons of record.

Given the lack of any additional argument to this rejection, Applicant is directed to the rebuttal above.

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 34-36 and 38-49 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-45 of copending Application No. 10/728,051. Although the conflicting claims are not identical, they are not patentably distinct from each other because an issuance of a patent to instant application drawn to a *genus* of composition comprising at least one modified allergen whose amino acid sequence differs from that of a wild-type allergen that occurs in nature such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified

allergen is encapsulated inside the dead *E. coli*; and a pharmaceutically acceptable carrier, wherein the wild-type allergen is found in nature in foods, in peanuts, milk, eggs, seafood, nuts, dairy products, fruit, as well as modified allergen is located in the cytoplasm or periplasm of the dead *E coli*, and means and mode of killing by heat, chemical treatment such as iodine, bleach, ozone or alcohol would include the pharmaceutical composition comprising dead *E coli* comprising at least one modified peanut allergen amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the wild-type peanut allergen is an Ara h 1, Ara h 2 or Ara h 3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: l, SEQ ID NO:2, or SEQ ID NO:3, and wherein the modified peanut allergen is encapsulated inside the dead *E. coli*; and a pharmaceutically acceptable carrier, as well as modified peanut allergen is located in the cytoplasm, or periplasm of dead *E coli*, and means and mode of killing by heat, chemical treatment such as iodine, bleach, ozone or alcohol of copending application 10/728,051.

Thus the issuance of a patent to instant application (genus) would include the pharmaceutical composition of 10/728,051 (specie). The issuance a patent to copending application 10/728,051 (species) anticipates the claimed composition of instant application (genus).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. The following new grounds of rejections are necessitated by the amendment filed October 21, 2008.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

12. Claims 34-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of various Genbank accession No. in claim 34 (see pages 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, and 27 of claim 34) is indefinite because the nucleotide sequence or amino acid sequences may change from time to time and yet it may continue to use the same Accession number. Further, some of the reference wild type sequences such as Pol e1 and Vesp c1 cited in the table of claim 34 are not even published, see page 19 of claim 34. As such, the metes and bounds of the claims cannot be determined.

Claims 35-49 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 34-36 and 39-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising dead *E. coli*. comprising at least one modified peanut allergen whose amino acid sequence is identical to that of a wild-type allergen Ara h1, Ara h2 or Ara h3, except that the modified allergen has at least one mutation in an IgE site such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen Ara h1 protein encoded by SEQ ID NO: 1, Ara h2 protein encoded by SEQ ID NO: 2 or Ara h3 encoded by SEQ ID NO: 3, wherein the modified allergen is encapsulated inside the dead *E. coli*; and a pharmaceutically acceptable carrier and a pharmaceutically acceptable carrier for treating peanut allergy, **does not** reasonably provide enablement for a composition comprising dead *E. coli*. comprising any "modified allergen", any modified food allergen, any modified peanut allergens other than Ara h1, Arah2 and Arah3, any modified milks allergen, any modified eggs, any modified seafood, any modified nuts, any modified dairy product, any modified fruit allergens, except that the modified allergen has at least one mutation in any IgE binding site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen wherein the modified allergen is encapsulated inside the dead E coli as set forth in claims 34-36 and 39-49 for treating or *preventing* undesirable allergic reactions and anaphylactic allergic reactions to peanut in a subject. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claims 34 and 39-49 are broadly drawn to a composition comprising dead *E. coli* comprising a genus of modified allergen whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen wherein modified allergen is encapsulated inside the dead *E. coli* and a pharmaceutical acceptable carrier.

Claim 35 is broadly drawn to a composition comprising dead *E. coli* comprising a subgenus of modified food allergen whose amino acid sequence is identical to that of a wild-type food allergen, except that the modified allergen has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen wherein modified allergen is encapsulated inside the dead *E. coli* and a pharmaceutical acceptable carrier.

Claim 36 is broadly drawn to a composition comprising dead *E. coli* comprising a subgenus of modified peanut allergen whose amino acid sequence is identical to that of a wild-type peanut allergen, except that the modified allergen has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen wherein modified allergen is encapsulated inside the dead *E. coli* and a pharmaceutical acceptable carrier.

Enablement is not commensurate in scope with claims as how to make any modified allergen mentioned above encapsulated inside the dead *E. coli* for a composition for treating or preventing any allergy, any allergy such as any food allergy.

At the time of filing, the specification discloses only modified peanut allergens Ara h1, Ara h2 and Ara h3 whose IgE site has at least one mutation in an IgE binding site such that the modified peanut allergen has reduced IgE binding, see page 49-50 Table 4-6. The specification discloses only the use of dead *E coli* as a delivery system to treat anaphylactic allergic reactions to peanut in a mouse subject. The methods of killing allergen-producing *E. coli* are heating at temperature ranging from 37 to 95 °C, by ethanol (0.1% to 10%), iodine (0.1% to 10%) and the most reproducible method of killing was heat at 60 °C for 20 minutes and does not denature or proteolyze the recombinant allergen(s) produced by said bacteria, see page 31. The intended use of the claimed pharmaceutical composition is to treat and to *prevent* peanut allergy. The specification discloses only modified peanut allergens Ara h1, Ara h2 and Arah3 wherein the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared to wild-type allergen Ara h1, Ara h2 or Ara h3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, respectively. Further, the specification at page 33 also discloses the levels of allergen release varied and was dependent on the expression vector and protein tested. In general, more Ara h2 was released than Ara h1 and Ara h3 (Ara h2 >>Ara h1>Ara h3). The instant specification at page 34 also discloses that "mice injected with *E. coli* producing Ara h 1 did not give detectable levels of any immunoglobulin to the Ara h 1 allergen and therefore, that data are not shown. Without limitation to theory, we speculate that this may be due to the relatively small amounts of Ara h 1 produced by these cells (see previous discussion). Mice injected with *E. coli* producing Ara h 2 contained relatively high levels of IgG1 and IgG2a. Again, without limitation to the cause, we speculated that this may be due to the amount of Ara h 2 released from these cells (see discussion above). Mice injected with *E. coli* producing Ara h 3 contained relatively high levels oflgG2a (indicative of a Thl-type response) and elicited relatively low levels of IgG1 (indicative of a Th2-type response".

At the time of filing, there is insufficient guidance as to the structure of any *modified allergen* without the amino acid sequence and where such amino acid sequence differs from the undisclosed wild-type allergen sequence. A protein without the amino acid sequence has no structure, much less function. Further, IgE epitope analysis using peptide fragments is useful when the antigen is recognized by patients' serum sequentially according to its primary sequence.

The specification does not describe the complete structure of any modified allergen, any modified Food allergen or any modified peanut allergens other than the modified peanut allergens Ara h1, Ara h2 and Ara h3 as shown in Table 4, 5 and 6, respectively.

Although amended claim 34 recites 325 different allergens include either GenBank accession numbers or references to published literature that describe these wild type sequences, the claims are drawn to a composition comprising dead E coli comprising any *modified* allergen, not wild type allergen encapsulated in dead *E coli*. There is no teachings regarding which amino acids within the IgE binding site among the genus of wild type allergen can vary and still result in reduced ability to bind to or cross-link IgE other than the modified peanut allergen Ara h1, Ara h2 and Ara h3. Further, it is noted that some of allergen sequence such as Pol e1 and Vesp c1 in the cited references are even unpublished, see amended claim 34, page 19 of the amendment filed Oct 21, 2008. Finally, none of the cited references discloses modified allergen that has at least one mutation in any IgE site.

With respect to the amended claim 34 recite GenBank Accession number, the nucleotide sequence or amino acid sequences submitted to GenBank may change from time to time and yet it may continue to use the same Accession number. As such, even the wild type sequence of the allergen is not adequately described, let alone the modified allergen using such sequence.

With respect to modified allergen differs from the wild-type allergen by one or more amino acid deletions, substitutions, or addition within any IgE binding site, the state of the art at the time of filing is such that IgE epitope on allergens are conformational. However, IgE mainly recognizes the conformation, but not the primary sequence of the allergen.

Aalberse et al (J Allergy Clin Immunol 106: 228-238, 2000; PTO 892) currently available data from crystallographic studies suggest that many IgE epitopes on allergens are conformational (see entire document, abstract, in particular). Given the existing knowledge in the art concerning IgE epitopes have high degree of variability within the genus of allergen, there is sufficient guidance as to which amino acid within the IgE binding site to be substituted, deleted, added or a combination thereof such that the claimed genus of modified allergen has reduced IgE binding.

As exemplified by the teachings of Burk et al (of record, Eur. J Biochem 245(2): 334-9, April 1997; PTO 1449) that "there is no obvious position within each peptide (IgE epitope) that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Burk et al teach modifying peanut allergen Ara h1 where the immunodominant IgE

binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an *increase* in IgE binding. Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* is useful for a composition for treating allergy.

Stanley *et al* (of record, Arch Biochem Biophys 342(2): 244-53, June 1997; PTO 1449) teach modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 of wild-type peanut allergen significantly reduced IgE binding while substitution of a serine residue at position 70 leads to an *increase* in IgE binding. Stanley *et al* conclude that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no *obvious position* within each peptide (IgE epitope) that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating allergy. Let alone for prevention of any allergy.

Rabjohn et al (of record, J Clinical Investigation 103(4): 535-542, 1999; PTO 1449) teach modified peanut allergen Ara h3. Rabjohn teach alanine substitution in wild-type peanut allergen Ara h3 at position 308, 309, 310, 311, 312, and 314 led to reduction of IgE binding. However, alanine substitution increases IgE binding at position 304 and 305 within the IgE binding epitope 4 (see page 540, col. 1, Table 2, in particular). Rabjohn et al conclude that "there was no obvious consensus in the type of amino acid that, when mutated to alanine, leads to complete loss or decrease in IgE binding" (see page 540, Mutations at specific residues eliminate IgE binding, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating allergy. Given the unlimited number of modified allergen, modified allergen in any foods, any food such as peanut and the limited in vivo working example, it is unpredictable which undisclosed modified allergen encapsulated inside the dead *E coli* in the claimed composition is effective for treating any allergy. Without the amino acid sequence of any and all modified allergen and the

corresponding the cDNA encoding said modified allergen, one of skilled in the art cannot make the recombinant modified allergen encapsulated inside the dead *E coli* for the claimed composition, let alone for *preventing* allergy in the absence of in vivo working example demonstrating such modified allergen could prevent any allergy.

Chatel et al, of record, teach various factors such as the nature of the allergen, the genetic background of mouse strain, the recombinant protein expressed influence the immune response to peanut allergen (see abstract, in particular). Chatel et al teach immune responses to proteins are known to be highly dependent on the nature of the allergen (see page 646, col. 1, first paragraph, in particular). Chatel et al teach immune response are also depends on the genetics of the mouse strain (see page 646, col. 1, fourth paragraph, in particular).

Gottieb et al, of record, teach the immune system of mice is also quite different from that of man (see page 894, col. 3, in particular). Given the unlimited number of modified allergens, modified food allergens, modified peanut allergens expressed in the dead *E coli* in the claimed composition, there is insufficient *in vivo* working example demonstrating the claimed composition is effective for treating any and all allergy.

Even if the wild-type peanut allergens are limited to Ara h1, and Ara h2 encoded by SEQ ID NO: 1 and 2, respectively, Kleber-Janke et al (Protein Expression and Purification 19: 419-424, 2000; PTO 892) teach the level of expression of peanut allergens using BL21(DE3) *Escherichia coli* host cells depends on the nature of the peanut allergen. Kleber-Janke et al teach cDNA encoding Ara h1 and Ara h2 subcloned into the expression vector pET-16b (Novagen) that uses the T7 RNA polymerase-responsive promoter resulted in *ineffective* expression of Ara h1, Ara h2 and Ara h6 in conventional BL21(DE3) *Escherichia coli* (see page 419, col. 2, first full paragraph, in particular). The reason for the ineffective expression of wild-type Ara h1, Ara h2 and Ara h6 in BL21(DE3) was due to high levels of AGG/AGA in Ara h1, Ara h2 and Ara h6 and the least use arginine codons AGG/AGA in *E. coli* (see abstract, page 419, col. 2, in particular).

Finally, the specification discloses immunizing mice with heat killed *E. coli* expressing three different recombinant peanut allergens resulted in three different outcomes (see page 34 of instant specification). In *re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed October 21, 2008 and February 29, 2008 have been fully considered but are not found persuasive.

Applicants' position is that the present specification includes the entire sequence of each of the wild type peanut allergens referred to in the claims (see, for example, SEQ ID NOs.: 2, 4, and 6); the specification also identifies or refers to the *known* IgE epitopes of each of these allergens (Tables 1-3 of the present specification). The specification also describes specific modifications of many of these IgE epitopes that reduce IgE binding (Tables 4-6 of the present specification). It is true that the specification does not specifically exemplify every possible mutation of every IgE epitope that can reduce IgE binding or cross-linking activity. However, as discussed during the interview, in light of the power of Molecular Biology, it is well within the purview of the person of ordinary skill to make other changes within these *precisely deigned* sequences and to test them to assess their effects on IgE binding or cross-linking. Such work is routine, even if laborious. Certainly, it the experimentation it requires is no more *undue* than that required in *In re Wands',* the legal standard for enablement.

As mentioned in Applicant's previous Response, the specification includes an appendix including an extensive list of various *wild type* allergens of many different types *(e.g.,* weed pollens, grass pollens, tree pollens, mites, animals, fungi, insects, foods, among others). All of the listed allergens (-325 different allergens) include either GenBank accession numbers or references to published literature that describe these sequences. As discussed during the Interview, one of ordinary skill in the art reading the specification would easily be able to apply the methods and principles explicitly exemplified in the specification to any of the -325 allergens in the appendix.

The specification goes into great detail characterizing three of these allergens *(i.e.,* Ara h 1, Ara h 2, and Ara h 3). Although these three proteins are all peanut allergens with *names* that sound similar to one another, they are in fact three very *different* proteins with *different* amino

acid sequences (SEQ ID NOs: 2, 4, and 6). Thus, the specification *describes and reduces to practice compositions and methods" relating to three distinct proteins.* For all of these reasons, Applicant respectfully submits that the specification is enabling and fully descriptive for *any* allergen.

The Examiner states that the specification does not provide enablement for a composition comprising dead *E. coli* comprising *any* modified allergen. For all of the reasons stated in Applicant's previous Response of February 29, 2008, Applicant does not agree with the Examiner's position. However, *solely* in order to further prosecution, and in spite of the fact that the Examiner failed to address any of Applicant's § 112 arguments from the previous Response, Applicant has amended claim 34 to recite the list of allergens presented in the Appendix that was originally filed with the present specification.

In response, claim 34 encompasses a composition comprising dead *E coli* comprising any one or more modified allergen whose amino acid sequence has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is encapsulated inside the dead E coli and a pharmaceutically acceptable carrier.

The specification discloses wild type unmodified peanut allergens Ara h1, Ara h2 and Ara h3 amino acid sequences now renumbered as SEQ ID NO: 81-83 encoded by nucleotide sequence of SEQ ID NO: 1, 2 and 3. The specification discloses IgE epitope within the peanut allergen Ara h1 protein (SEQ ID NO: 2) in Table 1, IgE epitope within the peanut allergen Ara h2 (SEQ ID NO: 4) in Table 2 and IgE epitope of peanut allergen Ara h3 in Table 3. The specification describes specific modifications of peanut allergen Ara h1, Ara h2 and Ara h3 IgE epitopes that reduce IgE binding, see Tables 4-6, respectively, of the present specification. Other than the modified peanut allergen Arah1, Arah2 and Ara h3, the specification does not adequately describe the structure of any modified allergen that has at least one mutation in any IgE binding site encapsulated in the dead *E coli* for the claimed composition. Given the modified allergen comprises one or more amino acid deletions, substitutions, or additions within any IgE binding site as compared to the wild-type allergen, the modified allergen has no resemblance to the wild type sequence.

The specification does not teach the complete structure of any *modified allergen*, any modified Food allergen or any modified peanut allergens other than the modified peanut allergens Ara h1, Ara h2 and Ara h3 as shown in Table 4, 5 and 6, respectively.

Although amended claim 34 recites 325 different allergens include either GenBank accession numbers or references to published literature that describe these sequences, the claims are drawn to a composition comprising dead E coli comprising any *modified* allergen, not wild type allergen encapsulated in dead *E coli*. There is no specific teachings regarding which amino acids within the binding site among the genus of wild type allergen sequence can vary and still result in reduced ability to bind to or cross-link IgE other than the modified peanut allergen Ara h1, Ara h2 and Ara h3. Further, it is noted that some of allergen sequence such as Pol e1 and Vesp c1in the cited references are unpublished, see amended claim 34, page 19 of the amendment filed Oct 21, 2008. None of the cited references discloses modified allergen that has at least one mutation in any IgE site.

With respect to the amended claim 34 recite GenBank Accession number, the nucleotide sequence or amino acid sequences submitted to GenBank may change from time to time and yet it may continue to use the same Accession number. As such, even the wild type sequence of the allergen is not adequately enabled, let alone the modified allergen using such sequence.

With respect to modified allergen differs from the wild-type allergen by one or more amino acid deletions, substitutions, or addition within any IgE binding site, the state of the art at the time of filing is such that IgE epitope on allergens are conformational. However, IgE mainly recognizes the conformation, but not the primary sequence of the allergen.

Aalberse et al (J Allergy Clin Immunol 106: 228-238, 2000; PTO 892) currently available data from crystallographic studies suggest that many IgE epitopes on allergens are conformational (see entire document, abstract, in particular). Given the existing knowledge in the art concerning IgE epitopes have high degree of variability within the genus of allergen, there is sufficient guidance as to which amino acid within the IgE binding site to be substituted, deleted, added or a combination thereof such that the claimed genus of modified allergen has reduced IgE binding.

As exemplified by the teachings of Burk et al (of record, Eur. J Biochem 245(2): 334-9, April 1997; PTO 1449) that "there is no obvious position within each peptide (IgE epitope) that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Burk et al teach modifying peanut allergen Ara h1 where the immunodominant IgE

binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an *increase* in IgE binding. Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* is useful for a composition for treating allergy.

Stanley *et al* (of record, Arch Biochem Biophys 342(2): 244-53, June 1997; PTO 1449) teach modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 of wild-type peanut allergen significantly reduced IgE binding while substitution of a serine residue at position 70 leads to an *increase* in IgE binding. Stanley *et al* conclude that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no *obvious position* within each peptide (IgE epitope) that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating allergy. Let alone for prevention of any allergy.

Rabjohn et al (of record, J Clinical Investigation 103(4): 535-542, 1999; PTO 1449) teach modified peanut allergen Ara h3. Rabjohn teach alanine substitution in wild-type peanut allergen Ara h3 at position 308, 309, 310, 311, 312, and 314 led to reduction of IgE binding. However, alanine substitution increases IgE binding at position 304 and 305 within the IgE binding epitope 4 (see page 540, col. 1, Table 2, in particular). Rabjohn et al conclude that "there was no obvious consensus in the type of amino acid that, when mutated to alanine, leads to complete loss or decrease in IgE binding" (see page 540, Mutations at specific residues eliminate IgE binding, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating allergy. Given the unlimited number of modified allergen, modified allergen in any foods, any food such as peanut and the limited in vivo working example, it is unpredictable which undisclosed modified allergen encapsulated inside the dead *E coli* in the claimed composition is effective for treating any allergy. Without the amino acid sequence of any and all modified allergen and the

corresponding the cDNA encoding said modified allergen, one of skilled in the art cannot make the recombinant modified allergen encapsulated inside the dead *E coli* for the claimed composition, let alone for *preventing* allergy in the absence of in vivo working example demonstrating such modified allergen could prevent any allergy.

Chatel et al, of record, teach various factors such as the nature of the allergen, the genetic background of mouse strain, the recombinant protein expressed influence the immune response to peanut allergen (see abstract, in particular). Chatel et al teach immune responses to proteins are known to be highly dependent on the nature of the allergen (see page 646, col. 1, first paragraph, in particular). Chatel et al teach immune response are also depends on the genetics of the mouse strain (see page 646, col. 1, fourth paragraph, in particular).

Gottieb et al, of record, teach the immune system of mice is also quite different from that of man (see page 894, col. 3, in particular). Given the unlimited number of modified allergens, modified food allergens, modified peanut allergens expressed in the dead *E coli* in the claimed composition, there is insufficient *in vivo* working example demonstrating the claimed composition is effective for treating any and all allergy.

Even if the wild-type peanut allergens are limited to Ara h1, and Ara h2 encoded by SEQ ID NO: 1 and 2, respectively, Kleber-Janke et al (Protein Expression and Purification 19: 419-424, 2000; PTO 892) teach the level of expression of peanut allergens using BL21(DE3) *Escherichia coli* host cells depends on the nature of the peanut allergen. Kleber-Janke et al teach cDNA encoding Ara h1 and Ara h2 subcloned into the expression vector pET-16b (Novagen) that uses the T7 RNA polymerase-responsive promoter resulted in *ineffective* expression of Ara h1, Ara h2 and Ara h6 in conventional BL21(DE3) *Escherichia coli* (see page 419, col. 2, first full paragraph, in particular). The reason for the ineffective expression of wild-type Ara h1, Ara h2 and Ara h6 in BL21(DE3) was due to high levels of AGG/AGA in Ara h1, Ara h2 and Ara h6 and the least use arginine codons AGG/AGA in *E. coli* (see abstract, page 419, col. 2, in particular).

Finally, the specification discloses immunizing mice with heat killed *E. coli* expressing three different recombinant peanut allergens resulted in three different outcomes (see page 34 of instant specification). In *re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors,

such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

With respect to the argument that one of skill in the art reading the specification would readily be able to apply the methods and principles explicitly exemplified in the specification, a method of screening is not a method of how to make. As such, the specification merely extends an invitation to one skill in the art to come up with the structure of the claimed modified allergen and test which undisclosed modified allergen when expressed in *E coli* and then render dead is useful for treating allergy. Note, limit claim 34 to modified peanut allergens Ara h1, Ara h2 and Ara h3 would obviate this rejection.

15. Claims 34-36 and 39-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 34 and 39-49 are broadly drawn to a composition comprising dead *E. coli* comprising a genus of modified allergen whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen wherein modified allergen is encapsulated inside the dead *E. coli* and a pharmaceutical acceptable carrier.

Claim 35 is broadly drawn to a composition comprising dead *E. coli* comprising a subgenus of modified food allergen whose amino acid sequence is identical to that of a wild-type food allergen, except that the modified allergen has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-

type allergen wherein modified allergen is encapsulated inside the dead *E. coli* and a pharmaceutical acceptable carrier.

Claim 36 is broadly drawn to a composition comprising dead *E. coli* comprising a subgenus of modified peanut allergen whose amino acid sequence is identical to that of a wild-type peanut allergen, except that the modified allergen has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen wherein modified allergen is encapsulated inside the dead *E. coli* and a pharmaceutical acceptable carrier.

Claim 38 encompasses a composition comprising dead *E. coli* comprising a species of modified peanut allergen whose amino acid sequence is identical to that of a wild-type peanut allergen Ara h1, Ara h2 or Ara h3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, except that the modified peanut allergen Ara h1, Ara h2 or Ara h3 has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen wherein modified allergen is encapsulated inside the dead *E. coli* and a pharmaceutical acceptable carrier.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence.

In this case, the specification does not reasonably provide a **written description** for any composition comprising dead *E. coli*. comprising at least any one "modified allergen", any modified allergen such as any modified allergens found in any foods, any peanut allergens other than modified peanut allergens Ara h1, Ara h2 and Ara h3, any modified milk, any modified eggs, any modified seafood, any modified nuts, any modified dairy products, any modified fruits, any modified venoms, or any modified latex whose amino acid sequence is identical to any wild-type allergen, except that the modified allergen has any mutation in an IgE site such that the

modified allergen has a reduced ability to bind to or cross-link as compared with the wild-type allergen as set forth in claims 34-36 and 39-49 for treating or *preventing* undesirable allergic reactions and anaphylactic allergic reactions with allergy in a subject.

At the time of filing, the specification discloses only modified peanut allergens Ara h1, Ara h2 and Ara h3 whose IgE site has at least one mutation in an IgE binding site such that the modified peanut allergen has reduced IgE binding, see page 49-50 Table 4-6. The modified peanut allergens are expressed in *E. coli* and render dead by heat. The specification discloses the use of dead *E coli* as a delivery system to treat anaphylactic allergic reactions to peanut in mice. The methods of killing allergen-producing *E. coli* are heating at temperature ranging from 37 to 95 °C, by ethanol (0.1% to 10%), iodine (0.1% to 10%) and the most reproducible method of killing was heat at 60 °C for 20 minutes and does not denature or proteolyze the recombinant allergen(s) produced by said bacteria, see page 31. The intended use of the claimed composition is to treat and to *prevent* any allergy. The instant specification at page 33 also discloses the level of allergen released varied and was dependent on the expression vector and protein tested. In general, more Ara h2 was released than Ara h1 and Ara h3 (Ara h2 >>Ara h1>Ara h3). The instant specification at page 34 also discloses that "mice injected with *E. coli* producing Ara h 1 did not give detectable levels of any immunoglobulin to the Ara h 1 allergen and therefore, that data are not shown. Without limitation to theory, we speculate that this may be due to the relatively small amounts of Ara h 1 produced by these cells (see previous discussion). Mice injected with *E. coli* producing Ara h 2 contained relatively high levels of IgG1 and IgG2a. Again, without limitation to the cause, we speculated that this may be due to the amount of Ara h 2 released from these cells (see discussion above). Mice injected with *E. coli* producing Ara h 3 contained relatively high levels oflgG2a (indicative of a Thl-type response) and elicited relatively low levels of IgG1 (indicative of a Th2-type response". The specification disclosed the complete structure of only three species of peanut allergen within the scope of the claimed modified peanut allergen Ara h1, Ara h2 and Ara h3 whose wild-type amino acid sequences are encoded by SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3. The specification discloses the reduction to practice of only three modified peanut allergens Ara h1, Ara h2 and Ara h3.

The specification does not describe other members of the modified food allergen or modified allergen by structure. The specification does not describe the complete structure of any modified allergen, any modified Food allergen or any modified peanut allergens other than the modified peanut allergens Ara h1, Ara h2 and Ara h3 as shown in Table 4, 5 and 6, respectively.

Common structural attribute, i.e. sequence of IgE binding sites of species of modified peanut Ara h1 allergen in the genus modified allergen are not described. The specification does not describe the common structure of any IgE binding site among the genus of modified wild-type allergen, the subgenus of modified food allergen and other species of modified peanut allergen. There is no teachings regarding which amino acids within the binding site among the genus of wild type allergen can vary and still result in reduced ability to bind to or cross-link IgE other than the modified peanut allergen Ara h1, Ara h2 and Ara h3. There is no disclosed correlation between structure and function.

Although amended claim 34 recites 325 different allergens include either GenBank accession numbers or references to published literature that describe these sequences, as stated previously, the claims are drawn to a composition comprising dead *E coli* comprising any *modified* allergen, not wild type allergen encapsulated in dead *E coli*. It is noted that some of allergen sequence such as Pol e1 and Vesp c1in the cited references are unpublished, see page 19 of claim 34. None of the cited references discloses modified allergen that has at least one mutation in any IgE site. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species), see MPEP 2163.

With respect to the amended claim 34 recite GenBank Accession number, the nucleotide sequence or amino acid sequences submitted to GenBank may change from time to time and yet it may continue to use the same Accession number. As such, even the wild type sequence of the allergen is not adequately described, let alone the modified allergen using such sequence.

With respect to modified allergen differs from the wild-type allergen by one or more amino acid deletions, substitutions, or addition within any IgE binding site, the modified allergen sequence has no resemblance to the wild type allergen sequence.

Vas-Cath, Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at

page 1116). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class, where the specification provided only the bovine sequence.

One of skill in the art would not recognize that applicants were in possession of a genus of modified allergen.

The state of the art at the time of filing is such that IgE epitope on allergens are conformational.

Aalberse et al (J Allergy Clin Immunol 106: 228-238, 2000; PTO 892) currently available data from crystallographic studies suggest that many IgE epitopes on allergens are conformational (see entire document, abstract, in particular).

While general knowledge in the art may have allowed one skill in the art to modify protein by random deletion, substitution, or addition, there is no census in the art about mutation in IgE epitope would led to reduce IgE binding or crosslinking.

Burk et al (of record, Eur. J Biochem 245(2): 334-9, April 1997; PTO 1449) teach that "there is no obvious position within each peptide (IgE epitope) that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Burk et al teach modifying peanut allergen Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an *increase* in IgE binding. Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* is useful for a composition for treating allergy.

Stanley *et al* (of record, Arch Biochem Biophys 342(2): 244-53, June 1997; PTO 1449) teach modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 of wild-type peanut allergen significantly reduced IgE binding while substitution of a serine residue at position 70 leads to an *increase* in IgE binding. Stanley *et al* conclude that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no *obvious position* within each peptide (IgE epitope) that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE

binding" (See page 251, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating allergy. Let alone for prevention of any allergy.

Rabjohn et al (of record, J Clinical Investigation 103(4): 535-542, 1999; PTO 1449) teach modified peanut allergen Ara h3. Rabjohn teach alanine substitution in wild-type peanut allergen Ara h3 at position 308, 309, 310, 311, 312, and 314 led to reduction of IgE binding. However, alanine substitution increases IgE binding at position 304 and 305 within the IgE binding epitope 4 (see page 540, col. 1, Table 2, in particular). Rabjohn et al conclude that "there was no obvious consensus in the type of amino acid that, when mutated to alanine, leads to complete loss or decrease in IgE binding" (see page 540, Mutations at specific residues eliminate IgE binding, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of any and all allergen when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating allergy.

Further, because the described modified peanut allergens in the dead *E coli* is not representative of the entire claimed genus of modified allergen encapsulated in the dead *E coli*, and the specification does not disclose structural features shared by members of the genus of modified allergen or the subgenus of modified food allergen, one of skill in the art would conclude that applicant was not in procession of the claimed genus because a description of only a composition comprising modified peanut allergen Ara h1, Ara h2 and Ara h3 expressed in dead *E coli* of this genus is not representative of the modified peanut allergen, or modified food allergen or modified allergen to show that the applicant would have been in possession of the claimed genus as a whole at the time of filing. Therefore, the specification fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the full scope of claims 34, 35 and 36.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115). Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1103, Friday April 11, 2004.

Applicants' arguments filed October 21, 2008 and February 29, 2008 have been fully considered but are not found persuasive.

Applicants' position is that the present specification includes the entire sequence of each of the wild type peanut allergens referred to in the claims (see, for example, SEQ ID NOs.: 2, 4, and 6); the specification also identifies or refers to the *known* IgE epitopes of each of these allergens (Tables 1-3 of the present specification). The specification also describes specific modifications of many of these IgE epitopes that reduce IgE binding (Tables 4-6 of the present specification). It is true that the specification does not specifically exemplify every possible mutation of every IgE epitope that can reduce IgE binding or cross-linking activity. However, as discussed during the interview, in light of the power of Molecular Biology, it is well within the purview of the person of ordinary skill to make other changes within these *precisely deigned* sequences and to test them to assess their effects on IgE binding or cross-linking. Such work is routine, even if laborious. Certainly, it the experimentation it requires is no more *undue* than that required in *In re Wands',* the legal standard for enablement.

As mentioned in Applicant's previous Response, the specification includes an appendix including an extensive list of various *wild type* allergens of many different types *(e.g.,* weed pollens, grass pollens, tree pollens, mites, animals, fungi, insects, foods, among others). All of the listed allergens (-325 different allergens) include either GenBank accession numbers or references to published literature that describe these sequences. As discussed during the Interview, one of ordinary skill in the art reading the specification would easily be able to apply the methods and principles explicitly exemplified in the specification to any of the -325 allergens in the appendix.

The specification goes into great detail characterizing three of these allergens *(i.e.,* Ara h 1, Ara h 2, and Ara h 3). Although these three proteins are all peanut allergens with *names* that sound similar to one another, they are in fact three very *different* proteins with *different* amino acid sequences (SEQ ID NOs: 2, 4, and 6). Thus, the specification *describes and reduces to practice compositions and methods" relating to three distinct proteins.* For all of these reasons, Applicant respectfully submits that the specification is enabling and fully descriptive for *any* allergen.

The Examiner states that the specification does not provide written description for a composition comprising dead *E. coli* comprising *any* modified allergen. For all of the reasons stated in Applicant's previous Response of February 29, 2008, Applicant does not agree with the

Examiner's position. However, *solely* in order to further prosecution, and in spite of the fact that the Examiner failed to address any of Applicant's § 112 arguments from the previous Response, Applicant has amended claim 34 to recite the list of allergens presented in the Appendix that was originally filed with the present specification.

In response, claim 34 encompasses a composition comprising dead *E coli* comprising any one or more modified allergen whose amino acid sequence has one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is encapsulated inside the dead E coli and a pharmaceutically acceptable carrier. The specification does not adequately describe what the IgE binding site of all allergen look like since the IgE site can be conformational or linear.

The specification discloses wild type unmodified peanut allergens Ara h1, Ara h2 and Ara h3 amino acid sequences now renumbered as SEQ ID NO: 81-83 encoded by nucleotide sequence of SEQ ID NO: 1, 2 and 3. The specification discloses IgE epitope within the peanut allergen Ara h1 protein (SEQ ID NO: 2) in Table 1, IgE epitope within the peanut allergen Ara h2 (SEQ ID NO: 4) in Table 2 and IgE epitope of peanut allergen Ara h3 in Table 3. The specification describes specific modifications of peanut allergen Ara h1, Ara h2 and Ara h3 IgE epitopes that reduce IgE binding, see Tables 4-6, respectively, of the present specification. Other than the modified peanut allergen Arah1, Arah2 and Ara h3, the specification does not adequately describe the structure of any modified allergen that has at least one mutation in any IgE binding site encapsulated in the dead *E coli* for the claimed composition. Given the modified allergen comprises one or more amino acid deletions, substitutions, or additions within any IgE binding site as compared to the wild-type allergen, the modified allergen has no resemblance to the wild type sequence. As such, the structure of the modified allergen in the claimed composition is not adequately described. The specification "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed.

With respect to the argument that the appendix and now the amended claim 34 recites 325 different allergens include either GenBank accession numbers or references to published literature that describe these sequences, as stated previously, it is noted that the claims are drawn to a composition comprising dead *E coli* comprising any *modified* allergen, not wild type allergen encapsulated in dead *E coli*. Further, it is noted that some of allergen sequence such as Pol e1 and Vesp c1in the cited references are unpublished, see page 19 of claim 34. None of the cited references discloses modified allergen that has at least one mutation in any IgE site. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species), see MPEP 2163.

With respect to the argument that the appendix and now the amended claim 34 recite GenBank Accession number, the nucleotide sequence or amino acid sequences submitted to GenBank may change from time to time and yet it may continue to use the same Accession number. As such, the wild type sequence of the allergen is not adequately described, let alone the modified allergen using such wild type sequence.

With respected to the argument that it is well within the purview of the person of ordinary skill to make other changes within these *precisely deigned* sequences and to test them to assess their effects on IgE binding or cross-linking. Such work is routine, even if laborious, Applicants appear to argue for enablement. This rejection is written description.

As of the filing of instant application, applicants are in possession of a composition comprising dead *E coli* comprising at least one modified peanut allergen selected from the group consisting of Ara h1, Ara h2 and Ara h3 wherein the modified peanut allergen is encapsulated inside the dead *E coli* for treating peanut allergy.

At the time of filing, applicants are NOT in procession of a genus of modified allergen encapsulated in side the dead *E coli* for the claimed composition for treating allergy.

The specification does not describe the common structure of any modified IgE binding site among the genus of wild-type allergen, the subgenus of modified food allergen and other species of modified peanut allergen. There is no specific teachings regarding which amino acids within the binding site among the genus of wild-type allergen listed in the Table of claim 34 can

vary and still result in reduced ability to bind to or cross-link IgE other than the modified peanut allergen Ara h1, Ara h2 and Ara h3.

There is no disclosed correlation between structure and function.

The state of the art at the time of filing is such that IgE epitope on allergens are conformational.

Aalberse et al (J Allergy Clin Immunol 106: 228-238, 2000; PTO 892) currently available data from crystallographic studies suggest that many IgE epitopes on allergens are conformational, not even linear (see entire document, abstract, in particular).

While general knowledge in the art may have allowed one skill in the art to modify protein by random deletion, substitution, or addition, there is no consensus in the art about mutation in IgE epitope would led to reduce IgE binding or crosslinking.

Burk et al (of record, Eur. J Biochem 245(2): 334-9, April 1997; PTO 1449) teach that "there is no obvious position within each peptide (IgE epitope) that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Burk et al teach modifying peanut allergen Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an *increase* in IgE binding. Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* is useful for a composition for treating allergy.

Stanley *et al* (of record, Arch Biochem Biophys 342(2): 244-53, June 1997; PTO 1449) teach modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 of wild-type peanut allergen significantly reduced IgE binding while substitution of a serine residue at position 70 leads to an *increase* in IgE binding. Stanley *et al* conclude that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no *obvious position* within each peptide (IgE epitope) that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in

turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating allergy. Let alone for prevention of any allergy.

Rabjohn et al (of record, J Clinical Investigation 103(4): 535-542, 1999; PTO 1449) teach modified peanut allergen Ara h3. Rabjohn teach alanine substitution in wild-type peanut allergen Ara h3 at position 308, 309, 310, 311, 312, and 314 led to reduction of IgE binding. However, alanine substitution increases IgE binding at position 304 and 305 within the IgE binding epitope 4 (see page 540, col. 1, Table 2, in particular). Rabjohn et al conclude that "there was no obvious consensus in the type of amino acid that, when mutated to alanine, leads to complete loss or decrease in IgE binding" (see page 540, Mutations at specific residues eliminate IgE binding, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating allergy.

Because the described modified peanut allergens Ara h1, Ara h2 and Ara h3 encapsulated in the dead *E coli* is not representative of the entire claimed genus of modified allergen, and the specification does not disclose structural features shared by members of the genus of modified allergen or the subgenus of modified food allergen, One skill in the art would recognize that applicants would not have been in possession of the claimed genus as a whole at the time of filing. Therefore, the specification fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the full scope of claims 34, 35 and 36.

Thus, the specification describes and reduces to practice compositions relating to three modified peanut allergen Ara h1, Ara h2 and Ara h3. Amending claim 34 to recite modified peanut allergen Ara h1, Ara h2 and Ara h3 would obviate this rejection.

16. No claim is allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

19. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
January 2, 2009